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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/716,349
Filing Date: November 17, 2003
Appellant(s): BERG ET AL.

Pamela J. Sherwood, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2 March 2009 appealing from the Office action mailed 25 September 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

A Notice of Appeal has been filed in related case, 10/220,999.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,801,859 Friend et al. 10-2004

Chung et al., Journal of Cell Biology, Vol. 95, p. 118-126, 1982

Rice et al., Analytical Biochemistry, Vol. 241, p.254-259, 1996

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites the limitation "the biological dataset profiles" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 22 is dependent from claim 17 in which a single dataset profile is produced. The method of claim 17 does not require the generation of multiple dataset profiles, thus claim 22 is vague with respect to the source of the other dataset profiles in addition to the one produced by the method of claim 17.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Friend et al. (US PAT 6,801,859), as evidenced by Chung et al. (Journal of Cell Biology, Vol. 95, p. 118-126, 1982).

Claim 17 is directed to a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound, wherein said culture comprises a plurality of factors in an amount sufficient to induce a plurality of pathways; measuring at least two parameters associated with said plurality of pathways and comparing the measurement of said at least two parameters with the measurement from a control cell culture lacking said compound, and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile, wherein said biological dataset profile is indicative of the pathways that are active in said cell culture.

Friend et al. teach a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound (col. 34, line 42-43); measuring at least two parameters associated with said plurality of pathways (col. 39, lines 32-33) and comparing (col. 39, lines 34-35) the measurement of

said at least two parameters with the measurement from a control cell culture lacking said compound (col. 39, line 31), and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile (col. 16, lines 32-35), wherein said biological dataset profile is indicative of the pathways that are active in said cell culture. Friend et al. teach the use of human kidney cells to evaluate drugs to generate consensus profiles (col. 10, line 56-59), reading on contacting cultured mammalian cells with a compound. Friend et al. shows that to measure drug response data, cell are exposed to graded levels of the drug or drug candidate of interest (col. 34, line 42-43).

It is inherent to the culture of mammalian cells to include a plurality of factors that affect a plurality of signaling pathways, as evidenced by Chung et al. who demonstrate the culturing of mammalian kidney cells in a culture medium having growth promoting amounts of factors such as epidermal growth factor and insulin, among others (p. 119, col. 1).

Regarding claim 22, Friend et al. teach the step of compiling a database of profiles (col. 24, lines 44-46).

As guided by the specification at [0094-0098], candidate agents of interest or candidate compounds are “biologically active agents that encompass numerous chemical classes, primarily organic molecules, which may include organometallic molecules, inorganic molecules, genetic sequences, etc.” Based on the guidance provided by the specification, the teaching of Friend et al. as evidenced by Chung et al.

of introducing a plasmid into cultured mammalian cells reads on the limitation of contacting a test mammalian cell culture with a compound (col. 45, line 1-10).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al. (US PAT 6,801,859), in view of Chung et al. (Journal of Cell Biology, Vol. 95, p. 118-126, 1982).

Claim 17 is directed to a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound, wherein said culture comprises a plurality of factors in an amount sufficient to induce a plurality of pathways; measuring at least two parameters associated with said plurality of pathways and comparing the measurement of said at least two parameters with the measurement from a control cell culture lacking said compound, and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile, wherein said biological dataset profile is indicative of the pathways that are active in said cell culture. In an embodiment, the cells are primary cells. In an embodiment, the culture medium includes at least one factor that

activates a pathway. In some embodiments, the culture medium include at least one factor that inhibits a pathway. In an embodiment, a profile database is compiled.

Friend et al. teach a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound (col. 34, line 42-43); measuring at least two parameters associated with said plurality of pathways (col. 39, lines 32-33) and comparing (col. 39, lines 34-35) the measurement of said at least two parameters with the measurement from a control cell culture lacking said compound (col.39, line 31), and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile (col. 16, lines 32-35), wherein said biological dataset profile is indicative of the pathways that are active in said cell culture. Friend et al. teach the use of human kidney cells to evaluate drugs to generate consensus profiles (col. 10, line 56-59), reading on contacting cultured mammalian cells with a compound. Friend et al. shows that to measure drug response data, cell are exposed to graded levels of the drug or drug candidate of interest (col. 34, line 42-43). Friend et al. teach cells derived from higher multi-cellular organisms (col. 6, lines 34-35) and cells derived from tissue (col. 44, line 66). In an embodiment, Friend et al. teach the step of compiling a database of profiles (col. 24, lines 44-46).

Friend et al. does not explicitly show primary cell lines. It is inherent that Friend's culture includes a plurality of factors inducing a plurality of signaling pathways as set forth above; however, Friend does not explicitly teach such factors.

Chung et al. shows a medium for culturing kidney cells. Chung et al. shows the medium includes insulin which promotes glucose uptake pathway, Epidermal Growth Factor (EGF) that activates the EGF receptor pathway, hydrocortisone is included in the medium(p. 119, col. 1). Chung et al. shows the liver cells are directly obtained from kidney tissue from Rabbit kidneys by a method of that is a combination of perfusion and digestion (p. 119, col. 1-2). Chung et al. shows primary cultures of rabbit kidney cells (p. 120, col.1). In an embodiment, Chung shows the inhibition of the alpha-methyl glucoside uptake pathway by the addition of phlorizin to the culture medium (p.125, col. 1, table II) Chung et al. shows advantageously that the culture of primary kidney cells with different growth factors provides a means for maintaining the distinct characteristics and morphologies of kidney cell types (p. 119, col. 1). Chung et al. shows hormonally-defined culture medium provides the benefit of significantly improving the culture conditions of primary kidney epithelial cells (p. 119, col. 1). In addition, Chung et al. shows that another benefit of hormonally-defined culture medium is that the primary kidney cells grown in the defined medium are have a closer resemblance to the tissue from which they are derived (p. 125, col. 2).

It would have been obvious to one of ordinary skill in the art to modify the method of Friend et al. who shows a method of screening compounds using cultured cell lines, the results of which are used to produce response profiles for compounds, with the kidney cell culture medium and primary kidney cell line of Chung et al. because Chung et al. shows hormonally-defined culture medium provides the benefit of significantly improving the culture conditions of primary kidney epithelial cells and the primary kidney

cells grown in the defined medium have a closer resemblance to the tissue from which they are derived.

Claims 17 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al. (US PAT 6,801,859), in view of Rice et al. (cited on IDS filed on 10/18/2005, NPL Ref. No. 2).

Claim 17 is directed to a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound, wherein said culture comprises a plurality of factors in an amount sufficient to induce a plurality of pathways; measuring at least two parameters associated with said plurality of pathways and comparing the measurement of said at least two parameters with the measurement from a control cell culture lacking said compound, and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile, wherein said biological dataset profile is indicative of the pathways that are active in said cell culture. In an embodiment, the cells are primary cells. In an embodiment, the culture medium includes at least one factor that activates a pathway. In some embodiments, the culture medium includes at least one factor that inhibits a pathway. In an embodiment, a profile database is compiled.

Friend et al. teach a method of analyzing a candidate compound for a biological activity of interest, comprising contacting a test cell culture with said compound (col. 34, line 42-43); measuring at least two parameters associated with said plurality of pathways (col. 39, lines 32-33) and comparing (col. 39, lines 34-35) the measurement of

said at least two parameters with the measurement from a control cell culture lacking said compound (col.39, line 31), and recording said measurements of said test cell culture and said control cell culture to produce a biological dataset profile (col. 16, lines 32-35), wherein said biological dataset profile is indicative of the pathways that are active in said cell culture. Friend et al. teach the use of human kidney cells to evaluate drugs to generate consensus profiles (col. 10, line 56-59), reading on contacting cultured mammalian cells with a compound. Friend et al. shows that to measure drug response data, cell are exposed to graded levels of the drug or drug candidate of interest (col. 34, line 42-43). Friend et al. teach cells derived from higher multi-cellular organisms (col. 6, lines 34-35) and cells derived from tissue (col. 44, line 66). Friend et al. teach the step of compiling a database of profiles (col. 24, lines 44-46).

Friend et al. doe not explicitly show primary cell lines. It is inherent that Friend's culture includes a plurality of factors inducing a plurality of signaling pathways as set forth above; however, Friend does not explicitly teach such factors.

Rice et al. shows the development of a high throughput screen to identify inhibitors of endothelial cell activation. Rice et al. shows that primary cells, HUVE cells, are used (p. 254, col. 2). Rice shows the primary cells in culture are contacted with a compound in which the media includes a plurality of factors (p. 255, col. 1). Rice et al. shows that the test culture includes the pathway activator IL-1beta (p. 257, col. 1). Rice et al. shows the test culture includes the pathway inhibitor, IL-1ra (p. 257, col. 1). Rice shows endothelial cells have a critical role in the inflammatory response contributing to

inflammatory disease and suggest that advantage of identifying inhibitors of endothelial cell activation will lead to useful therapeutics (p. 258, col. 2).

It would have been obvious to one of ordinary skill in the art to modify the method of Friend et al. who shows a method of screening compounds using cultured cell lines, the results of which are used to produce response profiles for compounds, with the primary cells and cytokine factors of Rice et al. because Rice et al. shows the role of endothelial cells activation in inflammatory diseases is critical and it would be advantageous to identify inhibitors of endothelial cell activation that will lead to useful therapeutics.

(10) Response to Argument

Regarding the rejection claim 22 as indefinite under 35 USC 112, Second Paragraph, appellant argues claim 22 is improperly rejected because the term “the biological dataset profiles" has antecedent basis in claim 17. The argument is not persuasive. Claim 22 recites “The method of claim 17, further including the step of compiling a plurality of the biological dataset profiles in a database.” Claim 17 recites “…recording the measurements of the test cell culture and the control cell culture to produce a biological dataset profile,…” in lines 9-10. Claim 17 results in a single biological dataset profile. Claim 17 does not provide proper antecedent basis for a plurality of the biological dataset profiles as claimed in claim 22. The rejection is maintained.

Regarding the rejection of claims 17 and 22 as anticipated by Friend et al. as evidenced by Chung et al. under 35 USC 102(e), appellant argues the rejection is improper because Friend et al. as evidenced by Chung et al. fails to show a cell culture including a plurality of factors inducing a plurality of pathways. Appellant states "The Friend et al. methods do not employ a cell culture comprising at least two factors or in which a plurality of pathways is activated" (Brief, filed 02 March 2009, p. 5, line 8-9). In response, it is noted that Friend et al. shows human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells (col. 10. line 56-59). Chung et al. provides the evidence that kidney cell culture requires the addition to the media of a plurality of factors. Chung et al. shows that primary kidney cultures from rabbit required media supplemented with three factors: insulin, transferrin, and hydrocortisone, for optimal growth (abstract, line 3-5). Each of insulin, transferrin, and hydrocortisone have receptors that distinctly target each of the factors and result in distinct signaling pathways. Chung discloses the use of hormonally defined medium as a means to maintain primary rabbit kidney cultures enriched for proximal-tubule cells (p. 119, col. 1, line 14-16). Chung illustrates this point in figure 3a showing that when any one of the insulin, hydrocortisone, or transferrin are removed from the culture medium of a pure proximal tubule culture, fewer viable cells exist in the media as compared to the control medium that contains insulin, hydrocortisone, and transferrin. Figure 3a also shows that the addition of EGF or T_3 to the culture medium of a pure proximal tubule culture also results in fewer cells. Chung et al. shows in figure 3b that when the same experiment is

performed using a mixed culture of cells taken from the whole kidney after 15 days, the deletion of transferrin or the addition of T_3, EGF or both, results in a proliferation of cells. Chung et al. concludes that kidney epithelial cells derived from different segments of the kidney (nephron) grow differently in response to hormones and growth factors (abstract, line 8-10). Thus the use of a plurality of factors to maintain cells of a particular type such as the kidney cells of Chung et al. and Friend et al. inherently require the use of a plurality of factors to maintain and grow the cells in culture.

Appellant argues that Friend et al. fails to disclose a method in which a test agent contacts cells in culture that stimulated in multiple pathways by the addition of at least 2 factors. Appellant's argument is not persuasive. Friend et al. shows that to measure drug response data, cells are exposed to graded levels of the drug or drug candidates of interest (col. 34, line 42-43).

Appellant argues that the factors contemplated by the methods of the instant claims are modulatory of specific pathways in order for the data set to be informative. The claims have been interpreted in light of the specification. The specification teaches at p. 12, paragraph [0035], line 1-3, that “assay combinations, usually employing cell cultures, are provided that simulate physiological cell states of interest, particularly physiological cell states in vivo, usually using the same type of cells or combinations of cells”. Chung shows “The proximal-tubule cells increased in number and maintained an epithelial morphology when cultured in serum-free medium supplemented with insulin, transferrin, and hydrocortisone.…The proximal-tubule cell cultures possess a number of characteristics typical of proximal tubules, including Na+-dependent a-methylglucoside

uptake, PTH-sensitive cyclic AMP synthesis, and the brush-border enzymes leucine amino peptidase,γ-glutamyl transpeptidase, and alkaline phosphatase" (p. 119, col. 1, lines 18-21 and 26-31). Chung shows the use of factors in culture media to maintain an environment that, as guided in the instant specification at [0035], "simulate physiological cell states of interest, particularly physiological cell states in vivo, usually using the same type of cells or combinations of cells".

Appellant mischaracterizes, at p. 7, lines 16-18 of the Brief filed 2 March 2009, the teaching of Friend et al. at col. 10, line 54-59 by stating, "The cited paragraph from column 10 suggests that screening drugs for treatment of kidney cancer might use kidney cancer cells, but that in preferred embodiments, yeast cells are used". Contrary to appellent's characterization, Friend et al. states at col. 10, line 54-59, "In most preferred embodiments of the invention, the cells used for cluster analysis are of the same type and from the same species as the species of interest. For example, human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells."

Regarding the rejection of claims 17 and 19-22 as unpatentable over Friend et al. in view of Chung et al. under 35 USC 103, Appellant splits the rejection of claims 17 and 19-22 in to 4 groups corresponding to the 4 claimed embodiments of the invention.

Regarding the arguments relating to group I, claims 17 and 22, appellant argues Friend et al. in view of Chung et al. fails to show a cell culture including a plurality of factors in which a plurality of pathways are induced. Appellant's argument is not

persuasive. Friend et al. shows human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells (col. 10. line 56-59). Chung et al. provides the evidence that kidney cell culture requires the addition to the media of a plurality of factors. Chung et al. shows that primary kidney cultures from rabbit required media supplemented with three factors, insulin, transferrin, and hydrocortisone, for optimal growth (abstract, line 3-5). Each of insulin, transferrin, and hydrocortisone has receptors that distinctly target each of the factors and result in distinct signaling pathways. Chung discloses the use of hormonally defined medium as a means to maintain primary rabbit kidney cultures enriched for proximal-tubule cells (p. 119, col. 1, line 14-16). Chung illustrates this point in figure 3a showing that when any one of the insulin, hydrocortisone, or transferrin are removed from the culture medium of a pure proximal tubule culture, fewer viable cells exist in the media as compared to the control medium that contains insulin, hydrocortisone, and transferrin. Figure 3a also shows that the addition of EGF or T_3 to the culture medium of a pure proximal tubule culture also results in fewer cells. Chung et al. shows in figure 3b that when the same experiment is performed using a mixed culture of cells taken from the whole kidney after 15 days, the deletion of transferrin or the addition of T_3, EGF or both, results in a proliferation of cells. Chung et al. concludes that kidney epithelial cells derived from different segments of the kidney (nephron) grow differently in response to hormones and growth factors (abstract, line 8-10). Thus, the use of a plurality of factors to maintain cells of a particular type such as the kidney cells

of Chung et al. and Friend et al. inherently require the use of a plurality of factors to maintain and grow the cells in culture.

Appellants argue that Friend et al. in view of Chung et al. fail to show the measurement of at least two parameters associated with a plurality of pathways. Appellants' argument is not persuasive. Friend et al. shows at col. 10, line 54-56 that "in most preferred embodiments of the invention, the cells used for cluster analysis are of the same type and from the same species as the species of interest. For example, human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells". As shown in Chung et al., kidney cells require specific factors for their growth in culture in *vitro*. Friend shows at col. 10, line 26-30 that the methods of the invention analyze response profiles which are obtained or provided from measurements of aspects of the biological state of the cell in response to a particular set or sets of perturbations, such as drug exposure. Friend et al. continues to show measurements are differential measurements of the change in cellular constituents in response to the drug (col. 10, line 36-37). Friend et al. calls the collected measurements response profiles (col. 10, line 38-41). Friend et al. shows cellular constituents in a biological response profile comprise genetic transcripts such as RNA abundances (col. 9, line 58-60). Thus, Friend et al. in view of Chung et al. shows the generation of a profile of the active pathways and their constituent components through measuring the response of cells cultured in a plurality of factors to a particular drug or test agent.

Appellant argues that the invention provides an unexpected benefit in that only when one compares a plurality of pathway way components can one distinguish the action of a test agent. Appellant's argument is not persuasive. Figure 3 of Friend et al. shows a similar analysis. In figure 3, Friend et al. shows a false color display of a plurality of genetic transcripts measured in a plurality of experiments. Friend et al. shows this has the benefit that the response profiles can be readily visualized (col. 28, line 58-59).

Appellants characterization of Friend et al. which occurs on p. 10 lines 19-36 of the brief filed 2 March 2009 are unrelated to Friend et al. as the citations by appellant do not appear to be found in Friend. The argument is confusing and thus unpersuasive.

Appellant argues that the methods of Friend et al. do not stimulate specific multiple pathways, compare results in the absence of agent, or involve determining pathways of action. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Friend shows at col. 10, line 26-30 that the methods of the invention analyze response profiles which are obtained or provided from measurements of aspects of the biological state of the cell in response to a particular set or sets of perturbations, such as drug exposure. Friend et al. shows human kidney cells are preferably tested to identify consensus profiles to evaluate drugs or therapies that are used to treat disorders involving human kidney cells (col. 10. line 56-59). Chung et al.

provides the evidence that kidney cell culture requires the addition to the media of a plurality of factors. Chung et al. shows that primary kidney cultures from rabbit required media supplemented with three factors, insulin, transferrin, and hydrocortisone, for optimal growth (abstract, line 3-5).

Appellant states Friend relies on a simplified cellular model provided by yeast. The statement is not accurate. Friend et al. teaches the biological effects of a drug are measured in the instant invention by observations of changes in the biological state of a cell, where a cell may be of any type; for example prokaryotic, eukaryotic, mammalian plant or animal (col. 7, line 25-29).

Appellant argues that unlike Friend et al., appellants' invention does not rely on co-varying or co-regulated constituents. The argument is not persuasive because similar to the claims, Friend et al obtains measurements of constituents in response to agents and compares the constituent measures to define sets of genes that are affected (co-regulated) by the agents to identify common responses between agents. This is similar to the data provided by appellant as table 1 on p. 9 in the Brief filed 02 March 2009, shows co-varying constituents, Il8 and,ICAM-1, in cells contacted with compounds N-acetylcysteine, prednisolone, and SB 203580.

Regarding the arguments relating to group II, claims 17 and 19, appellants argue that Friend et al. fails to show primary cells. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800

F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Friend et al. shows that kidney cells can be used to practice his invention. Chung et al. shows that primary kidney cells can be cultured in vitro. Chung et al. shows that in vitro studies of primary proximal tubule kidney cultures have the advantages of being more highly reproducible and may prove to have a closer resemblance to proximal tubule cells than any other available culture system (p. 125 col. 2, line 50- p. 126, col. 1, line 1).

Regarding the arguments relating to group III, claims 17 and 20, appellants argue Friend et al. fails to show a test culture comprising at least one activator of a pathway active in the cell culture. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Chung et al. shows that kidney test cell culture includes the cAMP activator PTH (parathyroid hormone) (p. 124, col. 1, lines 1-6).

Regarding the arguments relating to group III, claims 17 and 21, appellants argue Friend et al. fails to show a test culture comprising at least one inhibitor of a pathway active in the cell culture. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Chung et al. shows that kidney test cell culture includes the alpha-methylglucose uptake inhibitor phlorzin (p. 123, col. 2, line 3-7).

Regarding the rejection of claims 17 and 19-22 as unpatentable over Friend et al. in view of Chung et al. under 35 USC 103, Appellant argues Friend et al. in view of Rice et al. fails to teach the same limitations of the claims as argued for Friend et al. in view of Chung et al. Appellant's argument is not persuasive. Friend et al. teaches a method of analyzing the effects of drugs or agents on cells that are cultured. Friend et al. teaches cultured cells are contacted with an agent and the transcriptional state of genes or constituents are measured to produce biological response profiles (abstract, lines 1-5; col. 10, line 26-30; and col. 10, line 36-37). Friend does not explicitly show that cultured cells are stimulated with plurality of factors or that the cells are primary cells. Rice et al. shows that primary endothelial cells from human umbilical vein called HUVEC or Human Umbilical Endothelial Cells (p. 254, col. 2, line 30-32). Rice et al. shows the HUVEC cells are grown in a specialized medium called EGM that is supplemented with 2% serum (p. 255, col. 1, line 32-34). Both serum and plasma are obtained from blood, a well known transport medium for hormones, factors and other biologically active compounds in the body. It is also known in the art that serum is blood plasma lacking clotting agents. Serum is known to contain a plurality of biological factors which activate a plurality of pathways in cells. Rice et al. uses blood plasma in his experiments. Rice et al. shows the plasma contained a number of inflammatory agents such as IL-1β, TNFα, Il-6, and IL-8 in addition to the exogenously added LPS (p. 256, col. 1, line 14-16).

Appellant argues Rice et al. fails to show contacting cells that have been activated in multiple pathways with an agent; comparing results of activated cultures to cultures lacking test agent; analyzing multiple parameters; classification of agents by the pathway affected. The arguments are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding the argument that Rice et al. fails to show contacting cells that are activated in multiple pathways with an agent, it is noted that Friend et al. shows cells in culture are contacted with an agent as set forth above. Rice et al. shows that cells are grown in a media that is accepted in the art to contain a plurality of factors. Rice et al. further shows that plasma, or serum contains factors such as IL-1β, TNFα, Il-6, and IL-8 (p. 256, col. 1, line 14-16) may be added to a cell culture medium. Regarding the argument that Rice et al. fails to show the comparison of results between cells contacted with an agent and cells not contacted with an agent; it is noted that Friend et al. shows the biological state of the cells exposed to the drug and not exposed to the drug is measured (col. 34, line 53-55). To accomplish the measurement, Friend et al. uses 2-color fluorescence labeling to make a direct and internally controlled comparison of mRNA levels corresponding to each arrayed gene in two cell states (col. 39, line 52-60). Regarding the argument that Rice et al. fails to show the analysis of multiple parameters, it is noted that Friend et al. shows clustering algorithms to analyze arrays or matrices to determine dissimilarities

between cellular constituents, or parameters (col. 17, line 23-25). Regarding the argument that Rice et al. cannot classify an agent, it is noted that Friend et al. shows that classification is based on mechanisms of regulation. Friend et al. teaches cellular constituents can also be defined based upon the mechanism of the regulation of the cellular constituents (col. 23, line 17-20).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/KARLHEINZ R SKOWRONEK/

Examiner, Art Unit 1631

Conferees:

/Marjorie Moran/

Supervisory Patent Examiner, Art Unit 1631

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